Support for this amendment is found in the specification on page 6, line 19. Claims 6 and 10 have been amended to include the feature of methanol-inducible promoter, as previously called for in dependent claims 9 and 12. Claims 16 to 20 have been added. Support for claim 16 is found on page 9, line 14. Support for claims 17 and 18 is found on page 8, lines 17-18, and on page 10, line 19. Support for claims 19 and 20 is found on page 9, lines 15-19.

Rejections of the Claims

I. Rejection under 35 U.S.C. §112, second paragraph

Claims 4, 8, and 11 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for their recitation of the term "gla". These claims have been amended to replace the term "gla" with the term "glucoamylase". The term "gla" is an art recognized acronym for glucoamylase.

Applicants submit that the rejection of claims 4, 8, and 11 have been overcome by this amendment and the Examiner is requested to withdraw the rejection of these claims on this ground.

II. Rejection of the Claims over the Prior Art

A. Rejection under 35 U.S.C. §102(e)

The Examiner has rejected claims 1, 4, 6, 8, 10, and 11 under 35 U.S.C. §102(e) as being anticipated by the disclosure of Golightly, U.S. Patent No. 6,277,612. Applicants traverse the rejection of these claims on this ground.

As amended, independent claim 1, and claim 4 which depends therefrom, calls for the galactose oxidase being expressed in an inactive form. As amended, independent claims 6 and 10, and claims 8 and 11 which depend respectively from these claims, call for a methanol-inducible promoter. These features are neither disclosed nor suggested by the disclosure of Golightly.

Accordingly, Applicants submit that the claims as amended distinguish over Golightly and the Examiner is requested to withdraw the rejection of claims 1, 4, 6, 8, 10, and 11 on this ground.

B. Rejections under 35 U.S.C. §103(a)

1. Rejection of claims 1, 3, 5, 6, 7, 9, 10, and 12 over Golightly and Zamost

The Examiner has rejected claims 1, 3, 5, 6, 7, 9, 10, and 12 under 35 U.S.C. §103(a) as being obvious over the combined disclosure of Golightly, U.S. Patent No. 6,277,612, and Zamost, U.S. Patent No. 6,258,559. Applicants traverse the rejection of these claims on this ground.

Golightly discloses a method for producing galactose oxidase by expressing a DNA encoding galactose oxidase linked to a signal peptide. Zamost discloses methods for optimizing the production of recombinant proteins using the methylotrophic yeast host, *Pichia*. Zamost discloses a recipe for a growth medium for *Pichia*, the use of which overcomes problems faced by others using such a *Pichia* expression system. Zamost further discloses a listing of heterologous proteins that may be expressed from *Pichia*. See, column 21, lines 49-61.

Applicants submit that the combined disclosures of Golightly and Zamost neither disclose nor suggest the presently claimed invention and that there is no motivation for one of skill in the art to combine these two references, as was done by the Examiner in formulating the present rejection.

As discussed above, Golightly does not disclose the use of a methanol-inducible promoter or expression of a protein in an inactive form. In contrast, Zamost does disclose a methanol-inducible promoter, but discloses the use of such a promoter only in connection with the expression of proteins that are not inactivated when exposed to methanol.

As taught in the present specification, Applicants have discovered that expressing galactose oxidase in an inactive form according to the claimed method of the invention, such as by expression in the presence of methanol and which expression is induced by a methanol-inducible promoter, results in an increased yield of galactose oxidase and increased homogeneity of the galactose oxidase that is obtained.

Accordingly, Applicants submit that one skilled in the art would not combine the teaching of Golightly (expression of galactose oxidase) with the teaching of Zamost (*Pichia* with a methanol-inducible promoter). There is no suggestion in, or motivation provided by, the prior art to combine the teachings of these two references.

Accordingly, Applicants submit that the rejection of the claims as being obvious over the combined disclosure of Golightly and Zamost is overcome and the Examiner is requested to withdraw the rejection of these claims on this ground.

2. Rejection of claims 1 and 2 over Golightly and Montague-Smith

The Examiner has rejected claims 1 and 2 under 35 U.S.C. §103(a) as being obvious over the combined disclosure of Golightly, U.S. Patent No. 6,277,612, and Montague-Smith, Analytical Biochemistry, 207:353-355 (1992). Applicants traverse the rejection of these claims on this ground.

As discussed above, Golightly discloses a method for producing galactose oxidase by expressing a DNA encoding galactose oxidase linked to a signal peptide. Golightly discloses that the galactose oxidase is expressed in an active form. Montague-Smith discloses that galactose oxidase that is naturally secreted by the filamentous fungus *Dactylium dendroides* exists as a mixture of oxidized active and reduced inactive forms, which cannot be physically separated by standard purification techniques. Montague-Smith further discloses that this mixture of purified active and inactive enzyme may be treated with an oxidant, ferricyanide, to render active the entire sample of galactose oxidase.

Montague-Smith further discloses that enzyme that has been activated in this manner:

> is slowly reduced to a mixture of active and inactive forms, so that a large quantity of identical enzyme necessary for kinetic analyses cannot be maintained.

It is for this reason that Montague-Smith's disclosed method concerns activating or deactivating *small samples of enzymes*. See page 354, column 1, second paragraph, first sentence.

One major reason that enzyme which is activated according to the Montague-Smith method will degrade to the inactive form is that enzyme purified from *D. dendroides* is

associated with other molecules, including proteins. These other molecules render the activated enzyme unstable.

In contrast, the method of the invention provides stable recombinantly-produced galactose oxidase that is not associated with such other molecules and will not degrade over time to an inactive form.

New claims 19 and 20 call for an oxidation treatment that lasts longer than the 15 minutes disclosed by Montague-Smith. See, page 354, column 1, third paragraph, line 12. This is a further distinction over that of the prior art and provides a purer enzyme product than that of the prior art.

Applicants submit that neither of the two cited references, alone or in combination, disclose or suggest the presently claimed method of the invention. Accordingly, Applicants request that the rejection of claims 1 and 2 as being obvious over the combined disclosure of Golightly and Montague-Smith be withdrawn.

3. Rejection of claims 1, 4, 6, 8, 10 and 11 over McPherson and Ward

The Examiner has rejected claims 1, 4, 6, 8, 10, and 11 under 35 U.S.C. §103(a) as being obvious over the combined disclosure of McPherson, Journal of Biological Chemistry, 267(12):8146-8152 (1992), and Ward, WO 98/31821. Applicants traverse the rejection of these claims on this ground.

As stated by the Examiner, McPherson discloses a DNA encoding galactose oxidase, a vector comprising said DNA, and a method for producing galactose oxidase. The method disclosed by McPherson is by purifying the enzyme from a culture of the filamentous fungus

Dactylium dendroides, the fungus that naturally produces galactose oxidase. See, page 8147, column 1, first sentence. This method is that of the prior art described in the present specification on page 2. Disadvantages of this method are that the yield of galactose oxidase is very low and is associated with the secretion of biopolymers and other enzymes that complicate the isolation of pure galactose oxidase and inhibit the activation of galactose oxidase.

Combining this disclosure of McPherson with that of Ward does not disclose or suggest the present invention. In contrast to the statement by the Examiner on page 7, third paragraph, line 3 of the present Office Action, Ward does not disclose a transformed yeast. Rather, Ward teaches away from yeast, as is called for in the method of the present invention.

On page 19, first full paragraph, Ward distinguishes between filamentous fungi and yeasts. On line 5, Ward teaches that "Appropriate host cells include filamentous fungal cells." On lines 10 and 11, Ward teaches that "The filamentous fungi of the present invention are morphologically, physiologically, and genetically distinct from yeasts." On lines 16-19, Ward teaches that "Recent illustrations of differences between *S. cerevisiae* and filamentous fungi include the inability of *S. cerevisiae* to process *Aspergillus* and *Trichoderma* introns and the inability to recognize many transcriptional regulators of filamentous fungi."

Thus, Applicants submit that the combination of McPherson and Ward, each of which disclose the use of a filamentous fungus, does not disclose or suggest the method or the vector of the present invention as called for in claims 1 to 5 and 6 to 9, respectively, which call for a yeast. Significantly, the disclosure of Ward is a teaching away from yeast, as presently claimed.

Independent claim 10 has been amended to call for a "methanol-inducible promoter". Claim 11 depends from claim 10. Neither McPherson nor Ward disclose or suggest such a

promoter, the induction of which would render inactive the galactose oxidase that is the expression product of the nucleic acid.

Applicants submit that the claims, as amended, patentably distinguish over the combined disclosure of McPherson and Ward and request the Examiner to withdraw the rejection of claims 1, 4, 6, 8, 10, and 11 on this ground.

4. Rejection of claims 3, 5, 7, 9, and 12 over McPherson, Ward, and Zamost

The Examiner has rejected claims 3, 5, 7, 9, and 12 under 35 U.S.C. §103(a) as being obvious over the combined disclosure of McPherson, Journal of Biological Chemistry, 267(12):8146-8152 (1992), Ward, WO 98/31821, and Zamost, U.S. Patent No. 6,258,559. Applicants traverse the rejection of these claims on this ground.

The disclosures of McPherson and Ward are discussed above in the preceding section. Zamost discloses methods for optimizing the production of recombinant proteins using the methylotrophic yeast host, *Pichia*. Zamost discloses a recipe for a growth medium for *Pichia*, the use of which overcomes problems faced by others using such a *Pichia* expression system. Zamost further discloses a listing of heterologous proteins that may be expressed from *Pichia*. See, column 21, lines 49-61.

As discussed above, Zamost does not disclose the use of *Pichia* and a methanol-inducible promoter to express a protein, such as galactose oxidase, that is inactivated in the presence of methanol. Thus, Applicants submit that the combination of McPherson, Ward, and Zamost fails to disclose or suggest the present invention.

Moreover, Applicants submit that it is improper to combine a reference (Zamost) that discloses the use of yeast with a reference (Ward) that teaches away from the use of yeast. As stated in MPEP, §2143.01, there must be some suggestion or motivation to combine references in order to formulate a rejection for obviousness based upon such a combination. As in the present case, where one reference discloses yeast and a second reference teaches away from yeast, such suggestion or motivation is lacking.

Accordingly, Applicants submit that claims 3, 5, 7, 9, and 12 patentably distinguish over the prior art and the Examiner is requested to withdraw the rejection of these claims on this ground.

5. Rejection of claims 2 over McPherson, Ward, and Montague-Smith

The Examiner has rejected claim 2 under 35 U.S.C. §103(a) as being obvious over the combined disclosure of McPherson, Journal of Biological Chemistry, 267(12):8146-8152 (1992), Ward, WO 98/31821, and Montague-Smith, Analytical Biochemistry, 207:353-355 (1992). Applicants traverse the rejection of these claims on this ground.

The disclosures of McPherson and Ward are discussed in the preceding two sections. The disclosure of these two references is limited to filamentous fungi. Montague-Smith discloses that galactose oxidase that is naturally secreted by the filamentous fungus *Dactylium dendroides* exists as a mixture of oxidized active and reduced inactive forms, which cannot be physically separated by standard purification techniques. Montague-Smith further discloses that this mixture of purified active and inactive enzyme may be treated with an oxidant, ferricyanide, to render active the entire sample of galactose oxidase.

Applicants submit that these references, alone or in combination, fail to disclose the invention called for in claim 2. The present invention calls for the expression of galactose oxidase utilizing a transformed yeast. Each of the three cited references discloses a filamentous fungus. Ward teaches away from yeast. Thus, Applicants submit that claim 2 is patentably distinguishable over the prior art.

Moreover, as discussed above, the disclosure of Montague-Smith relating to activation of galactose oxidase is insufficient to render claim 2 obvious. The prior art does not disclose or suggest the method of claim 1, from which claim 2 depends, in which galactose oxidase is expressed in an inactive form.

Accordingly, Applicants submit that the claim 2 patentably distinguishes over the prior art and the Examiner is requested to withdraw the rejection of this claim on this ground.

CONCLUSION

Applicants submit that the present claims, as amended, are in condition for allowance and request an early notification to that effect.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on January 27, 2003.

Dated: 1/27/03

Howard M. Eisenberg

Appendix

Amendments to the Claims

1. (Amended) A method for producing isolated galactose oxidase comprising transforming a yeast with a vector comprising a nucleic acid sequence encoding a fusion protein of a signal peptide and galactose oxidase, and an inducible promoter that regulates transcription of the sequence encoding said fusion protein, culturing said transformed yeast, inducing said promoter to cause yeast to produce said fusion protein, removing within the yeast said signal peptide from the galactose oxidase, and secreting the galactose oxidase from the yeast, wherein the galactose oxidase is in an inactive form when secreted from the yeast.

4. (Amended) The method of claim 1 wherein the signal peptide is an *Aspergillus niger* [*gla*] glucoamylase signal peptide.

6. (Amended) A vector for transforming yeast comprising a nucleotide sequence encoding a fusion protein of a signal peptide and galactose oxidase, and a[n] methanol-inducible promoter that regulates transcription of the sequence encoding said fusion protein.

8. (Amended) The vector of claim 6 wherein the signal peptide is an *Aspergillus niger* [*gla*] glucoamylase signal peptide.

10. (Amended) A nucleotide sequence encoding a fusion protein of a signal peptide and galactose oxidase, and a[n] methanol-inducible promoter that regulates transcription of the sequence encoding said fusion protein.

11. (Amended) The nucleotide sequence of claim 10 wherein the signal peptide is an *Aspergillus niger* [*gla*] glucoamylase signal peptide.